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Dated: May 3, 2007 Signature: (Isatta B. Smith)



Docket No.: JJJ-P01-514
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Sampath et al.

Application No.: 09/445,328 Confirmation No.: 9813

Filed: December 7, 1999 Art Unit: 1647

For: THERAPIES FOR ACUTE RENAL FAILURE Examiner: D. S. Romeo

## APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This responds to the Notice of Non-Compliant Appeal Brief dated April 18, 2007. The deadline for filing an amended Appeal Brief is one month from the date of mailing of the Notice, or May 18, 2007. Accordingly, this amended Appeal Brief is timely filed, and is in furtherance of the Notice of Appeal filed on December 8, 2006.

Payment of fees required under § 41.20(b)(2) is authorized in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37:

## I. REAL PARTY IN INTEREST

The real parties in interest for this appeal are as follows:

Curis, Inc., the owner of the application, and Johnson & Johnson, the licensee of the application.

## II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

To the best of the knowledge of the undersigned, there are no other appeals, interferences or judicial proceedings known to the Appellant, the Appellant's legal representative, or the above-noted real party of interest that will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

## III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 45 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 1, 3, 4, 7, 10, 13, 39-52
2. Claims withdrawn from consideration but not canceled: 21, 22, 25, and 28-34
3. Claims pending: 2, 5, 6, 8, 9, 11, 12, 14-20, 23, 24, 26, 27, 35-38, and 53-65
4. Claims allowed: None
5. Claims objected: None
6. Claims rejected: 2, 5, 6, 8, 9, 11, 12, 14-38, and 53-65

C. Claims On Appeal

The claims on appeal are claims 2, 5, 6, 8, 9, 11, 12, 14-38, and 53-65.

## IV. STATUS OF AMENDMENTS

An amendment was filed on December 8, 2006 in response to the Final Office Action dated September 21, 2006. The Examiner entered the amendment as indicated in the Advisory Action dated January 18, 2007.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

Applicants provide the following concise summary of the subject matter defined in each of the independent claims involved in the appeal, with appropriate page and line numbers referring to the cited portions of the originally-filed specification:

Claim 2

The methods and compositions of this invention capitalize in part upon the discovery that certain proteins of eukaryotic origin, defined herein as OP/BMP renal therapeutic agents, and including members of the osteogenic protein/bone morphogenetic protein (OP/BMP) family of proteins, may be used in the treatment of subjects in, or at risk of, acute renal failure. (page 2, line 33-36). Useful renal therapeutic agents include polypeptides, or functional variants of polypeptides, comprising at least the C-terminal six-or seven-cysteine domain of a mammalian protein selected from the group consisting of OP-1, OP-2, OP-3, BMP2, BMP3, BMP4, BMP5, BMP6, BMP9, and proteins which exhibit at least 70% or, more preferably, 75% or 80% amino acid sequence homology with the amino acid sequence of the seven-cysteine domain of human OP-1; and are (a) capable of inducing chondrogenesis in the Reddi-Sampath ectopic bone assay (Sampath and Reddi (1981), Proc. Natl. Acad. Sci. (USA) 78:7599-7603) or a substantially equivalent assay, (b) capable of significantly preventing, inhibiting, delaying or alleviating the permanent or progressive loss of renal function which may result from acute renal failure in a standard animal model of acute renal failure, or (c) capable of causing a clinically significant improvement in a standard marker of renal function when administered to a mammal in, or at risk of, acute renal failure.

(page 2, line 36 to page 3, line 10). The renal therapeutic agents of the present invention may be evaluated for their therapeutic efficiency in causing a clinically significant improvement in a standard marker of renal function when administered to a mammalian subject. (page 11, lines 5-7).

Claim 53

The methods and compositions of this invention capitalize in part upon the discovery that certain proteins of eukaryotic origin, defined herein as OP/BMP renal therapeutic agents, and including members of the osteogenic protein/bone morphogenetic protein (OP/BMP) family of proteins, may be used in the treatment of subjects in, or at risk of, acute renal failure. (page 2, line 33-36). The renal therapeutic agents useful herein include therapeutically effective proteins in which the amino acid sequences comprise a sequence sharing at least 60% amino acid sequence identity, and preferably, 65% or 70% identity with the C-terminal seven cysteine domain present in the active forms of human OP-1. (page 9, lines 9-13). The renal therapeutic agents of the present invention may be evaluated for their therapeutic efficiency in causing a clinically significant improvement in a standard marker of renal function when administered to a mammalian subject. (page 11, lines 5-7)

Claim 58

The methods and compositions of this invention capitalize in part upon the discovery that certain proteins of eukaryotic origin, defined herein as OP/BMP renal therapeutic agents, and including members of the osteogenic protein/bone morphogenetic protein (OP/BMP) family of proteins, may be used in the treatment of subjects in, or at risk of, acute renal failure. (page 2, line 33-36). The renal therapeutic agents useful herein include therapeutically effective proteins in which the amino acid sequences comprise a sequence sharing at least 60% amino acid sequence identity, and preferably, 65% or 70% identity with the C-terminal seven

cysteine domain present in the active forms of human OP-1. (page 9, lines 9-13). Useful renal therapeutic agents include polypeptides, or functional variants of polypeptides, comprising at least the C-terminal six-or seven-cysteine domain of a mammalian protein selected from the group consisting of OP-1, OP-2, OP-3, BMP2, BMP3, BMP4, BMP5, BMP6, BMP9, and proteins which exhibit at least 70% or, more preferably, 75% or 80% amino acid sequence homology with the amino acid sequence of the seven-cysteine domain of human OP-1; and are (a) capable of inducing chondrogenesis in the Reddi-Sampath ectopic bone assay (Sampath and Reddi (1981), Proc. Natl. Acad. Sci. (USA) 78:7599-7603) or a substantially equivalent assay, (b) capable of significantly preventing, inhibiting, delaying or alleviating the permanent or progressive loss of renal function which may result from acute renal failure in a standard animal model of acute renal failure, or (c) capable of causing a clinically significant improvement in a standard marker of renal function when administered to a mammal in, or at risk of, acute renal failure. (page 2, line 36 to page 3, line 10). The renal therapeutic agents of the present invention may be evaluated for their therapeutic efficiency in causing a clinically significant improvement in a standard marker of renal function when administered to a mammalian subject. (page 11, lines 5-7). Generally speaking, acute renal failure may be due to pre-renal, post-renal, or intrinsic renal causes. (Page 1, lines 20-21). As used herein, pre-renal causes of acute renal failure include decreased cardiac output, hypovolemia, volume redistribution, and altered vascular resistance. (page 4, lines 29-31).

Claim 61

The methods and compositions of this invention capitalize in part upon the discovery that certain proteins of eukaryotic origin, defined herein as OP/BMP renal therapeutic agents, and including members of the osteogenic protein/bone morphogenetic protein (OP/BMP) family of proteins, may be used in the treatment of subjects in, or at risk of, acute renal failure. (page 2, line 33-36). The renal

therapeutic agents useful herein include therapeutically effective proteins in which the amino acid sequences comprise a sequence sharing at least 60% amino acid sequence identity, and preferably, 65% or 70% identity with the C-terminal seven cysteine domain present in the active forms of human OP-1. (page 9, lines 9-13). Useful renal therapeutic agents include polypeptides, or functional variants of polypeptides, comprising at least the C-terminal six-or seven-cysteine domain of a mammalian protein selected from the group consisting of OP-1, OP-2, OP-3, BMP2, BMP3, BMP4, BMP5, BMP6, BMP9, and proteins which exhibit at least 70% or, more preferably, 75% or 80% amino acid sequence homology with the amino acid sequence of the seven-cysteine domain of human OP-1; and are (a) capable of inducing chondrogenesis in the Reddi-Sampath ectopic bone assay (Sampath and Reddi (1981), Proc. Natl. Acad. Sci. (USA) 78:7599-7603) or a substantially equivalent assay, (b) capable of significantly preventing, inhibiting, delaying or alleviating the permanent or progressive loss of renal function which may result from acute renal failure in a standard animal model of acute renal failure, or (c) capable of causing a clinically significant improvement in a standard marker of renal function when administered to a mammal in, or at risk of, acute renal failure. (page 2, line 36 to page 3, line 10). The renal therapeutic agents of the present invention may be evaluated for their therapeutic efficiency in causing a clinically significant improvement in a standard marker of renal function when administered to a mammalian subject. (page 11, lines 5-7). Generally speaking, acute renal failure may be due to pre-renal, post-renal, or intrinsic renal causes. (Page 1, lines 20-21). As used herein, pre-renal causes of acute renal failure include decreased cardiac output, hypovolemia, volume redistribution, and altered vascular resistance. (page 4, lines 29-31). Administration is expected to be continuous or frequent (e.g., daily) during the period of acute renal failure, typically 1-3 weeks, but may also be continued for several weeks or months after the acute phase. (page 3, lines 15-17).

Claim 64

The methods and compositions of this invention capitalize in part upon the discovery that certain proteins of eukaryotic origin, defined herein as OP/BMP renal therapeutic agents, and including members of the osteogenic protein/bone morphogenetic protein (OP/BMP) family of proteins, may be used in the treatment of subjects in, or at risk of, acute renal failure. (page 2, line 33-36). The renal therapeutic agents useful herein include therapeutically effective proteins in which the amino acid sequences comprise a sequence sharing at least 60% amino acid sequence identity, and preferably, 65% or 70% identity with the C-terminal seven cysteine domain present in the active forms of human OP-1. (page 9, lines 9-13). Useful renal therapeutic agents include polypeptides, or functional variants of polypeptides, comprising at least the C-terminal six-or seven-cysteine domain of a mammalian protein selected from the group consisting of OP-1, OP-2, OP-3, BMP2, BMP3, BMP4, BMP5, BMP6, BMP9, and proteins which exhibit at least 70% or, more preferably, 75% or 80% amino acid sequence homology with the amino acid sequence of the seven-cysteine domain of human OP-1; and are (a) capable of inducing chondrogenesis in the Reddi-Sampath ectopic bone assay (Sampath and Reddi (1981), Proc. Natl. Acad. Sci. (USA) 78:7599-7603) or a substantially equivalent assay, (b) capable of significantly preventing, inhibiting, delaying or alleviating the permanent or progressive loss of renal function which may result from acute renal failure in a standard animal model of acute renal failure, or (c) capable of causing a clinically significant improvement in a standard marker of renal function when administered to a mammal in, or at risk of, acute renal failure. (page 2, line 36 to page 3, line 10). The renal therapeutic agents of the present invention may be evaluated for their therapeutic efficiency in causing a clinically significant improvement in a standard marker of renal function when administered to a mammalian subject. (page 11, lines 5-7). Generally speaking, acute renal failure may be due to pre-renal, post-renal, or intrinsic renal causes. (Page 1, lines 20-21). As used herein, pre-renal causes of acute renal failure

include decreased cardiac output, hypovolemia, volume redistribution, and altered vascular resistance. (page 4, lines 29-31). In some cases, however, the subjects may present with other symptoms (e.g. osteodystrophy) for which renal therapeutic agent treatment would be indicated. (page 12, lines 5-6).

Although those teachings are summarized above, the Board is strongly urged to study the specification before considering the rejections on appeal.

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The single ground of rejection to be reviewed on appeal is whether independent claims 2, 53, 58, 61 and 64 satisfy the nonobviousness requirement of 35 U.S.C. 103(a).

Claims 2 and 53 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kubersampath (WO 93/04692) and Lefer (J Mol Cell Cardiol. 1992 Jun; 24(6):585-93).

Claim 58, 61 and 64 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) in view of Kubersampath (WO 93/04692), Lefer (J Mol Cell Cardiol. 1992 Jun;24(6):585-93), Anderson (Chapter 275, in Harrison's Principles of Internal Medicine, 1980) and Brady (Chapter 236, in Harrison's Principles of Internal Medicine, 1994).

## VII. ARGUMENT

For the convenience of the Board, Table A below is provided indicating the relationship between the elements of the five independent claims (claims 2, 53, 58, 61, and 64) under appeal.

**Table A**: Comparison of Claim Elements of Claims under Appeal

| Claims | Agent | Cause of Acute Renal Failure | Agent Administration | Subjects being Treated |
|---|---|---|---|---|
| 2 | 70% homologous to OP-1 Seven-Cys Domain | ANY | ANY | ANY |
| 53 | 60% identical to OP-1 Seven-Cys Domain | ANY | ANY | ANY |
| 58 | 70% homologous OR 60% identical to OP-1 Seven-Cys Domain | Pre-Renal | ANY | ANY |
| 61 | 70% homologous OR 60% identical to OP-1 Seven-Cys Domain | Pre-Renal | Continuously for 1-3 weeks | ANY |
| 64 | 70% homologous OR 60% identical to OP-1 Seven-Cys Domain | Pre-Renal | ANY | Afflicted with Osteodystrophy |

Appellants note that a pre-renal cause of acute renal failure was elected as the species for search purposes. While claims 2 and 53 relate to any form of acute renal failure, claim 58 recites pre-renal causes of acute renal failure. As a result, Appellants have grouped claims 2, 53 and 58 for the appeal as standing and falling together. To simplify this appeal, appellants select claim 58 from this group of three claims to be argued in this appeal.

Claims 61 and 64 will be argued separately since they recite at least one element not found in any one of claims 2, 53, or 58. Nevertheless, if the Board agrees with Appellants that claim 58 is nonobvious over the cited references, then claims 61 and 64 should also be deemed nonobvious since they incorporate all the elements found in claim 58.

*CLAIM 58*

The Examiner rejects claim 58 as being allegedly obvious over Kelly (J Clin Invest. 1996 Feb 15;97(4):1056-63) ("Kelly") in view of Kubersampath (WO 93/04692) ("Kubersampath") and Lefer (J Mol Cell Cardiol. 1992 Jun; 24(6):585-93) ("Lefer"). Claims that depend from claim 58 are rejected in further view of Anderson (Chapter 275, in Harrison's Principles of Internal Medicine, 1980) ("Anderson") and Brady (Chapter 236, in Harrison's Principles of Internal Medicine, 1994) ("Brady").

The Examiner's argument for rejecting claim 58 may be outlined as follows:

(1) Kelly suggests that agents that block ICAM-adhesiveness or that block polymorphonuclear cell (PMC) activity might be effective in treating acute renal failure.

(2) Kubersampath teaches that the morphogen OP-1 is an anti-inflammatory agent that blocks ICAM adhesiveness.

(3) Lefer teaches that OP-1 is an anti-inflammatory agent that inhibits PMC activity.

(4) Therefore, one skilled in the art would expect that the anti-inflammatory OP-1 would be successful in treating acute renal failure.

The Examiner, then, assumes that if agent X is known to reduce inflammation, then one skilled in the art would reasonably expect that agent X would be effective in treating acute renal failure. Based on this central assumption, the Office Action concludes that since OP-1 is allegedly effective in treating inflammation then one skilled in the art would reasonably expect OP-1 to be effective in treating acute renal failure.

As will be shown below, this argument fails because at the time the subject application was filed, anti-inflammatory agents were known to *decrease* renal function, or even to cause outright renal failure, when administered to subjects. In particular, Transforming Growth Factor Beta 1(TGFβ1), Cyclosporin A (CsA) and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

were documented in the scientific and medical literature to *decrease* renal function when administered to a subject. This clearly teaches away from use of anti-inflammatories in the treatment of acute renal failure. Accordingly, one skilled on the art would have expected that administration of the anti-inflammatory OP-1 to a mammal afflicted with acute renal failure would have aggravated, not improved, renal function in the mammal. In other words, one skilled in the art would not have had a reasonable expectation that OP-1, or other morphogens, would be effective in treating acute renal failure.

(1) A Reasonable Expectation of Success is Lacking for the Use of OP-1 to Improve Renal Function in Subjects Afflicted with Acute Renal Failure

MPEP 706.02(j) sets forth three basic criteria needed to establish a *prima facie* case of obviousness: 1) the prior art references must teach or suggest all the claim limitations; 2) some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) a reasonable expectation of success.

At least the third prong is not satisfied in this case. The Examiner has failed to show why one skilled in the art would have ignored the scientific literature documenting the adverse renal effects of anti-inflammatory agents, and why he would have selected the anti-inflammatory agent OP-1 to improve renal function in a subject with renal dysfunction (i.e. with acute renal failure). In fact, one skilled in the art would have expected that the morphogen OP-1 would not only fail to improve renal function in a subject afflicted with acute renal failure, but also that it would aggravate the renal dysfunction. The skilled artisan would not have expected OP-1 to be the exception among anti-inflammatory agents.

(2) Anti-Inflammatory Drugs were Known to be Detrimental to Renal Function

At the time the application was filed, it was well-documented in the scientific literature that anti-inflammatory agents reduced, rather than improved, renal function.

On pages 10-16 of the Amendment filed on November 12, 2004, Applicants established that Transforming Growth Factor Beta 1(TGFβ1), Cyclosporin A (CsA) and Nonsteroidal Anti-

Inflammatory Drugs (NSAIDs) were known at the time the subject application was filed to be both (i) anti-inflammatory agents which inhibit ICAM adhesiveness, and (ii) *detrimental* to renal function. The November 12, 2004 amendment included thirteen scientific publications, as Exhibits A-M, documenting the anti-inflammatory and the renal-adverse side effects of these three agents. Rather than reproducing this section of the previous office action in this appeal brief, Appellants provide a summary of the documented adverse renal effects of these three agents in Table B below. The Board is nevertheless encouraged to review the arguments and the Exhibits as provided in the November 12, 2004 amendment in their entirety.

**Table B**. Documented adverse kidney effects of anti-inflammatory agents

| Agent | Exhibit # | Finding |
|---|---|---|
| TGFβ1 | D | "Recent studies show that TGF-beta overexpression in experimental and human kidney diseases leads to progressive glomerular and tubulointerstitial scarring and renal failure," (Abstract)<br>"New therapies may prevent progressive fibrosis in chronic kidney disease by suppressing the action of TGF-beta." (Abstract) |
| | F | "Overproduction of TGF-beta is the cause of pathologic matrix accumulation in the nephritic glomeruli" (Abstract)<br>"Studies of humans with glomerulonephritis and diabetic nephropathy also strongly implicated TGF-beta in the pathogenesis of glomerular matrix build-up" (Abstract) |
| CsA | I | "Cyclosporine A causes an acute reduction in GFR." (Abstract) (GFR stands for Glomerular Filtration Rate, a primary measure of renal function |
| NSAIDs | K | "Approximately 1-5% of people who are exposed to a nonsteroidal anti-inflammatory drug (NSAID) will manifest one of a variety of renal function abnormalities ... Renal abnormalities include fluid and electrolyte disturbances, acute deterioration of renal function, nephritic syndrome with interstitial nephritis, and papillary necrosis" (Page 588, columns 1-2)<br>"from the clinical point of view, the most worrisome renal side effect of NSAIDs is hemodynamically mediated acute renal failure, which occurs in individuals with pre-existing reduced renal blood perfusion" (Page 588, column 2) |
| | L | "Patients with pre-existing risk factors are susceptible to potentially life-threatening toxicities [form NSAIDs], including acute renal failure (ARF) and serious fluid and electrolyte disorders" (page S-61, column 1) |
| | M | "Among persons with normal renal function, who have no other risk |

| | | |
|---|---|---|
| | | factors (dehydration) for an acute hemodynamic effect, there is no risk. However, NSAID administration to susceptible persons may cause decrements in renal plasma flow and glomerular filtration rate within hours" (Abstract) |

(3) One skilled in the Art Would Have Expected that Administration of OP-1 to a Mammal Afflicted with Acute Renal Failure Would Reduce, not Increase, Renal Function

OP-1 shares two key properties with TFGβ1, CsA and NSAIDs: (i) it decreases ICAM adhesiveness and (ii) it decreases PMC activity. OP-1 and TFGβ1 are also members of the TFGβ superfamily of growth factors. The Examiner has focused exclusively on OP-1's anti-inflammatory property as the key attribute in making it a seemingly successful candidate for treating Acute Renal Failure (ARF).

But at the time the application was filed, anti-inflammatory agents were documented to actually cause renal dysfunction, especially in subjects with already impaired renal function. One skilled in the art would have expected that OP-1, just like its counterpart anti-inflammatory agents TFGβ1, CsA and NSAIDs, would further impair renal function in a subject afflicted with acute renal failure. One skilled in the art would have expected that administration of the anti-inflammatory OP-1 polypeptide, based on its anti-inflammatory and neutrophil adhesion-inhibiting properties that it shares with NSAIDs, would reduce, rather than increase, renal function. If anything, the documented anti-renal effects of anti-inflammatory agents taught away from administering anti-inflammatory agents, such as OP-1, to subjects with impaired renal function.

While having the burden of proof, the Examiner has failed to establish why one skilled in the art would have made OP-1 the exception amongst anti-inflammatory agents. He has failed to show why one would have expected OP-1 to be the anomaly and to actually improve renal function where other anti-inflammatory agents failed. The burden of going forward was and is on the Examiner to overcome the presumption of lack of reasonable expectation of success legitimately established by applicant using documentary evidence during prosecution. Because he has failed to do so, he has failed to establish a *prima facie* case of obviousness in accordance with MPEP 706.02(j).

(4) The Examiner's Counterarguments Fail to Address Why OP-1 Would Have Been Expected to Be the Exception Among Anti-inflammatory Agents

In response to Appellants arguments, the Examiner alleges that there is no evidence of record that OP-1 possesses any of the renal side effects of TGFβ1, CsA or NSAIDS. The Examiner claims that applicants have not met a burden of proof in providing a nexus between (i) anti-inflammatory agents inhibiting ICAM adhesiveness and (ii) anti-inflammatory agents being detrimental to acute renal function. But the burden is on the Examiner, not on applicants, to establish the third prong of the *prima facie* case of obviousness. It is the Examiner who must present evidence why one skilled on the art would have expected a fourth anti-inflammatory agent (OP-1) to be the exception among anti-inflammatories – to show why a fourth anti-inflammatory would be effective in treating acute renal failure when the three others anti-inflammatory agents impair renal function. The Examiner wants Appellants to provide evidence that OP-1 had the adverse renal effects of the other anti-inflammatory agents. But this is impossible because Appellants discovered that, contrary to expectation, OP-1 could improve renal function.

The Examiner has made some additional rebuttals on previous Office Actions, but none of them address the heart of the matter: why would OP-1 be the exception among anti-inflammatory agents? Some of these rebutting arguments are as follows:

(i) The Examiner alleges that despite the evidence showing the ineffectiveness of anti-inflammatories in treating ARF, one could not have known for sure whether OP-1 would fail in treating ARF until it was actually tested. The Examiner's position turns the test for obviousness on its head. The standard is the reasonable expectation that the invention would work successfully, and not whether there was the infinitesimal chance that OP-1 might improve renal function contrary to expectation. Indeed, since there is no evidence supplied by the Examiner that OP-1 would be effective in treating ARF, and documentary evidence shows that other anti-inflammatories were ineffective, there is no *prima facie* case of obviousness.

(ii) The Examiner points to differences between OP-1 and TGFβ1 in bone formation to suggest that the two molecules might have different biological properties in treating other organs. The question, however, is not whether the possibility exists, no matter how small, that two

compounds can have different properties. The question is what properties one skilled in the art would have expected the morphogens to have and why one would have expected OP-1 to be an exception. Merely pointing out that OP-1 is a different compound than TGFβ1, CsA or an NSAID, proves nothing. TGFβ1, CsA or an NSAID all have different structures from each other yet they all reduce inflammation and reduce renal function. The common teaching of such prior art is that anti-inflammatories generally have an adverse effect on renal function. The claimed invention runs counter to conventional wisdom.

(iii) The Examiner seeks to prematurely shift the burden of proof to Applicants, when the Examiner's own initial burden of proof has not yet been satisfied. Specifically, the Examiner is requiring applicants to prove that OP-1 would not be expected to exhibit the harmful renal effects of other anti-inflammatory agents, when it is the Examiner who bears the initial burden of showing why OP-1 should be considered as the exception amongst anti-inflammatory agents. MPEP 2142 imposes the initial burden on the examiner, and this burden has not been meet.

*CLAIM 61*

As indicated in the preceding section, a reasonable expectation of success has not been established for claim 58. Claim 61 is identical to claim 58 except that it further recites "wherein the agent is administered continuously during the period of acute renal failure" and "wherein the period of acute renal failure lasts from one to three weeks." Therefore, the failure to establish a reasonable expectation of success for the method of claim 58 also applies to the method of claim 61, thus rendering claim 61 nonobvious.

A failure to establish a *prima facie* case of obviousness for claim 61 also arises from the failure of the Examiner to establish a basis as to how the combination of cited references teaches or suggests all the elements of claim 61. In particular, the Examiner has not shown how the combination of cited references allegedly teaches (i) the treatment of a period of acute renal failure lasting from only one to three weeks; and (ii) the continuous administration of OP-1 during this one to three week period of acute renal failure.

Rather than specifically pointing out how these two elements are allegedly taught by the combination of references, the Examiner merely alleges that "the differences between the

teachings of the references relied upon and the limitations of claims 60-65 would have been obvious absent any evidence that these differences are unexpected and unobvious" (page 3, lines 6-8 of the Office Action dated September 26, 2006). A single circular conclusory statement, however, is insufficient to satisfy the Examiner's burden of establishing a *prima facie* case of obviousness under MPEP § 706.02(j). The Examiner must specifically point out how all the elements of claim 61, including the two cited above, are allegedly taught by the combination of references, must point out how the references could be combined to achieve the claimed method, and must point out why one skilled in the art would have had a reasonable expectation of success in treating acute renal failure by administering the morphogen only during a period of one to three weeks. Since the Examiner has failed to show meet these three burdens, a *prima facie* case of obviousness has not been made.

*CLAIM 64*

As indicated in the preceding section, a reasonable expectation of success has not been established for claim 58. Claim 64 is identical to claim 58 except that it further recites "wherein the mammal is afflicted with osteodystrophy." Therefore, the failure to establish a reasonable expectation of success for the method of claim 58 also applies to the method of claim 64, rendering claim 64 also nonobvious.

A failure to establish a *prima facie* case of obviousness also arises from the failure of the Examiner to establish a basis as to how the combination of cited references teaches or suggests the treatment of a subject afflicted with osteodystrophy as recited in claim 64.

The Examiner has not identified any teachings or suggestions in the combination of cited references for treating subjects who are additionally afflicted with osteodystrophy. Instead, the Examiner impermissibly tries to use the specification itself as one of the 103(a) references. The Examiner claims to use "the specification as a dictionary for [the] definition of subjects for treatment" (page 3, lines 20-21 of the Office Action dated September 21, 2006), and concludes that it would have been obvious to treat a subject afflicted with osteodystrophy.

But it is the combination of cited reference, and not the specification of the subject application, that must teach or suggest all the claim elements. This section of the specification

states that "[i]n some number of cases, however, the subjects may present with other symptoms (e.g. osteodystrophy) for which morphogen treatment would be indicated." (page 12, lines 5-6). The Examiner cannot use the specification as a reference against itself. The suggestion or teaching to treat subjects afflicted with osteodystrophy must be found in the prior art. And the section of the specification cited by the Examiner is not providing any type of definition. It is showing embodiments of subjects that may be treated with OP-1.

The Examiner has failed to meet his burden of establishing why treatment of ARF patients additionally afflicted with osteodystrophy is allegedly taught by the prior art, and therefore has failed to make a *prima facie* case of obviousness under MPEP § 706.02(j).

CONCLUSION

In sum, the Examiner has not established a *prima facie* case of obviousness since he failed to show a reasonable expectation of success for using anti-inflammatory morphogens to improve renal function because anti-inflammatory agents were expected to do the opposite: to decrease renal function, i.e., the prior art teaches away from the present invention. Therefore, all independent claims are nonobvious over the cited references, including claims 58, 61 and 64. Furthermore, for claims 61 and 64, the Examiner has failed to show how the cited references teach or suggest all their claim elements.

Applicant believes no fee is due for the filing of this Appeal Brief. However, if fee is due, please charge our Deposit Account No. 18-1945, under Order No. JJJ-P01-514 from which the undersigned is authorized to draw.

Dated: May 3, 2007

Respectfully submitted,

By_____

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## VIII. CLAIMS APPENDIX

The claims involved in the present appeal are shown below. Canceled claims are not shown. No claims are presently allowed.

2. A method of effecting an improvement in a standard marker of renal function in a mammal afflicted with acute renal failure, the method comprising administering to said mammal a therapeutically effective amount of an OP/BMP renal therapeutic agent comprising a polypeptide comprising a sequence at least 70% homologous to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of human OP-1 being set forth at residues 330-431 of human OP-1, wherein said renal therapeutic agent:

(a) induces chondrogenesis in an ectopic bone assay; or

(b) prevents, inhibits, delays or alleviates loss of renal function resulting from acute renal failure in an animal model of acute renal failure;

thereby effecting an improvement in a standard marker of renal function in the mammal afflicted with acute renal failure.

5. The method of claim 2 or 53, wherein said renal therapeutic agent comprises a polypeptide consisting of at least a C-terminal cysteine domain of a protein selected from the group consisting of a pro form, a mature form, and a soluble form of a polypeptide selected from the group consisting of OP-1, OP-2, OP-3, BMP2, BMP3, BMP4, BMP5, BMP6, and BMP9.

6. The method as in claim 5, wherein said renal therapeutic agent comprises a polypeptide consisting of at least a C-terminal cysteine domain of a protein selected from the group consisting of a pro form, a mature form, and a soluble form of human OP-1.

8. The method of claim 2, wherein said polypeptide has at least 75% homology with an amino

acid sequence of a seven-cysteine domain of human OP-1.

9. The method of claim 2, wherein said polypeptide has at least 80% homology with an amino acid sequence of a seven-cysteine domain of human OP-1.

11. The method of claim 53, wherein said polypeptide has at least 65% identity with an amino acid sequence of a seven-cysteine domain of human OP-1.

12. The method of claim 53, wherein said polypeptide has at least 70% identity with an amino acid sequence of a seven-cysteine domain of human OP-1.

14. The method of claim 2 or 53, wherein said renal therapeutic agent is selected from the group consisting of human osteogenic proteins and human bone morphogenic proteins.

15. The method of claim 2 or 53, wherein serial determination of BUN in said mammal indicates a rate of increase in BUN of at least 2 to 4 mmol/L/day (5 to 10 mg/dL/day).

16. The method of claim 2 or 53, wherein serial determination of BUN in said mammal indicates a rate of increase in BUN of at least 4 to 8 mmol/L/day (10 to 20 mg/dL/day).

17. The method of claim 2 or 53, wherein serial determination of serum creatinine in said mammal indicates a rate of increase in serum creatinine of at least 20 to 40 μmol/L/day (0.25 to 0.5 mg/dL/day).

18. The method of claim 2 or 53, wherein serial determination of serum creatinine in said mammal indicates a rate of increase in serum creatinine of at least 40 to 80 μmol/L/day (0.5 to 1.0 mg/dL/day).

19. The method of claim 2 or 53, wherein said mammal is afflicted with acute renal failure caused by a pre-renal cause, a post-renal cause, or an intrinsic renal cause.

20. The method of claim 19, wherein said mammal is afflicted with acute renal failure caused by a pre-renal cause selected from the group consisting of decreased cardiac output, hypovolemia, volume redistribution, and altered vascular resistance.

21. The method of claim 19, wherein said mammal is afflicted with acute renal failure caused by a post-renal cause selected from the group consisting of ureteral, pelvic and bladder obstructions.

22. The method of claim 19, wherein said mammal is afflicted with acute renal failure caused by an intrinsic renal cause selected from the group consisting of abnormalities of the vasculature, abnormalities of the glomeruli, acute interstitial nephritis, intratubular obstruction, renal artery occlusion and acute tubular necrosis.

23. The method of claim 2 or 53, wherein said mammal is a kidney transplant recipient.

24. The method of claim 2 or 53, wherein said mammal possesses only one kidney.

25. The method of claim 2 or 53, wherein said administration is oral.

26. The method of claim 2 or 53, wherein said administration is parenteral.

27. The method of claim 2 or 53, wherein said administration is intravenous.

28. The method of claim 2 or 53, wherein said administration is intraperitoneal.

29. The method of claim 2 or 53, wherein said administration is into the renal capsule.

30. The method of claim 26, wherein a stent has been implanted into said mammal for said administration.

31. The method of claim 30, wherein said stent is an intravenous stent.

32. The method of claim 30, wherein said stent is an intraperitoneal stent.

33. (The method of claim 30, wherein said stent is a renal intracapsular stent.

34. The method of claim 26, wherein said administration is by an implanted device.

35. The method of claim 2 or 53, wherein said administration is daily for a period of at least about one week.

36. The method of claim 2 or 53, wherein said administration is at least once a week for a period of at least about one month.

37. The method of claim 2 or 53, wherein said renal therapeutic agent is administered at a dosage of about 0.01-1000 μg/kg body weight of said mammal.

38. The method of claim 37, wherein said renal therapeutic agent is administered at a dosage of about 0.1-100 μg/kg body weight of said mammal.

53. A method of effecting an improvement in a standard marker of renal function in a mammal afflicted with acute renal failure, the method comprising administering to said mammal a therapeutically effective amount of an OP/BMP renal therapeutic agent comprising a polypeptide comprising a sequence at least 60% identical to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of human OP-1 being set forth at residues 330-431 of human OP-1, wherein said renal therapeutic agent:

(a) induces chondrogenesis in an ectopic bone assay; or

(b) prevents, inhibits, delays or alleviates loss of renal function resulting from acute

renal failure in an animal model of acute renal failure;

thereby effecting an improvement in a standard marker of renal function in the mammal afflicted with acute renal failure.

54. The method of claim 53, wherein the standard marker of kidney function is a rate of increase in BUN levels, rate of increase in serum creatinine, static measurement of BUN, static measurement of serum creatinine, glomerular filtration rate (GFR), ratio of BUN/-creatinine, serum concentration of sodium (Na+), urine/plasma ratio for creatinine, urine/plasma ratio for urea, urine osmolarity, or daily urine output.

55. The method of claim 2, wherein the standard marker of kidney function is a rate of increase in BUN levels, rate of increase in serum creatinine, static measurement of BUN, static measurement of serum creatinine, glomerular filtration rate (GFR), ratio of BUN/creatinine, serum concentration of sodium (Na+), urine/plasma ratio for creatinine, urine/plasma ratio for urea, urine osmolarity, or daily urine output.

56. The method of claim 2, wherein administration of the OP/BMP renal therapeutic agent delays the need for, or reduces the frequency of, dialysis treatments of the mammal afflicted with acute renal failure.

57. The method of claim 53, wherein administration of the OP/BMP renal therapeutic agent delays the need for, or reduces the frequency of, dialysis treatments of the mammal afflicted with acute renal failure.

58. A method of effecting an improvement in a standard marker of renal function in a mammal afflicted with acute renal failure, the acute renal failure being one arising from a pre-renal cause of acute renal failure, the method comprising administering to said mammal a therapeutically effective amount of an OP/BMP renal therapeutic agent comprising a polypeptide comprising a sequence at least 60% identical or 70%

homologous to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of human OP-1 being set forth at residues 330-431 of human OP-1, wherein said renal therapeutic agent:

(a) induces chondrogenesis in an ectopic bone assay; or

(b) prevents, inhibits, delays or alleviates loss of renal function resulting from acute renal failure in an animal model of acute renal failure;

thereby effecting an improvement in a standard marker of renal function in the mammal afflicted with acute renal failure arising from a pre-renal cause of acute renal failure.

59. The method of claim 58, wherein the pre-renal cause of acute renal failure is selected from decreased cardiac output, hypovolemia, volume redistribution, and altered vascular resistance.

60. The method of claim 58, wherein the agent is administered continuously during the period of acute renal failure.

61. A method of effecting an improvement in a standard marker of renal function in a mammal afflicted with acute renal failure, the acute renal failure being one arising from a pre-renal cause of acute renal failure, the method comprising administering to said mammal a therapeutically effective amount of an OP/BMP renal therapeutic agent comprising a polypeptide comprising a sequence at least 60% identical or 70% homologous to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of human OP-1 being set forth at residues 330-431 of human OP-1, wherein said renal therapeutic agent:

(a) induces chondrogenesis in an ectopic bone assay; or

(b) prevents, inhibits, delays or alleviates loss of renal function resulting from acute renal failure in an animal model of acute renal failure;

wherein the agent is administered continuously during the period of acute renal failure, wherein the period of acute renal failure lasts from one to three weeks,

thereby effecting an improvement in a standard marker of renal function in the mammal afflicted with acute renal failure arising from a pre-renal cause of acute renal failure.

62. The method of claim 58, wherein the acute renal failure is characterized by a deterioration of renal function over a period of a few days.

63. The method of claim 58, wherein serial determination of serum creatinine in said mammal indicates a rate of increase in serum creatinine exceeding 100 mg/dL/day.

64. A method of effecting an improvement in a standard marker of renal function in a mammal afflicted with acute renal failure, the acute renal failure being one arising from a pre-renal cause of acute renal failure, the method comprising administering to said mammal a therapeutically effective amount of an OP/BMP renal therapeutic agent comprising a polypeptide comprising a sequence at least 60% identical or 70% homologous to the C terminal seven-cysteine domain of human OP-1, the sequence of the C terminal seven-cysteine domain of human OP-1 being set forth at residues 330-431 of human OP-1, wherein said renal therapeutic agent:

(a) induces chondrogenesis in an ectopic bone assay; or

(b) prevents, inhibits, delays or alleviates loss of renal function resulting from acute renal failure in an animal model of acute renal failure;

wherein the mammal is afflicted with osteodystrophy,

thereby effecting an improvement in a standard marker of renal function in the mammal afflicted with acute renal failure arising from a pre-renal cause of acute renal failure.

65. The method of claim 58, wherein the mammal requires continuous hemodialysis sessions.

## IX. EVIDENCE APPENDIX

No evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the Examiner is being submitted.

## X. RELATED PROCEEDINGS APPENDIX

No related proceedings are referenced in section II above. Therefore, copies of decisions in related proceedings do not exist; hence none are included.

5-7-07

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# TRANSMITTAL FORM

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|---|---|
| Application Number | 09/445,328 |
| Filing Date | December 7, 1999 |
| First Named Inventor | Kuber T. Sampath et al. |
| Art Unit | 1647 |
| Examiner Name | David S. Romeo |
| Total Number of Pages in This Submission | |
| Attorney Docket Number | JJJ-P01-514 |

## ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
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- ☐ Proprietary Information
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| Firm Name | Fish & Neave IP Group Ropes & Gray LLP | | |
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| Printed name | Spencer H. Schneider | | |
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# TRANSMITTAL FORM

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## ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
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- ☐ Amendment/Reply
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- ☐ Affidavits/declaration(s)
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- ☐ Information Disclosure Statement
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- ☐ Reply to Missing Parts/ Incomplete Application
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- ☐ Landscape Table on CD
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- ☐ Appeal Communication to Board of Appeals and Interferences
- ☒ Appeal Communication to TC **(Amended Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
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| Firm Name | Fish & Neave IP Group Ropes & Gray LLP | | |
| Signature | | | |
| Printed name | Spencer H. Schneider | | |
| Date | 5-3-07 | Reg. No. | 45,923 |

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